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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,593	01/25/2002	Ralf Geiben Lynn	23659-502	2936

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,593	LYNN ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12062002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 12 August, 2004, wherein claims 4-17 were canceled without prejudice or disclaimer, claims 1 and 2 amended, and new claims 18 and 19 submitted. Claims 1-3, 18, and 19 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement filed 06 December, 2002, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-3, 18, and 19 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *In re Rochester*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004). The claims have been amended to recite a method of treating HIV-1

infection through the administration of a "naturally occurring peroxiredoxin" selected from the peroxiredoxin families I-IV. As previously set forth the term "peroxiredoxin" is defined in the specification to encompasses allelic variants, species variants, and conservative amino acid substitution variants. The term also encompasses peroxiredoxin fragments (pp. 10-11, bridging paragraph). Thus, a reasonable interpretation of the claim language, based upon the definitions set forth in the specification, would encompass all of these species.

As previously set forth, in order to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of variant peroxiredoxins. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir.

1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406

(Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

As previously set forth, the claims of the instant application are broadly directed toward variant peroxiredoxins. The term peroxiredoxin can encompass allelic variants, species variants, conservative amino acid substitution variants, fragments, substitutions, deletions, insertions, inversions or cyclisations. The peroxiredoxin family encompasses a large and diverse number of sundry proteins (e.g., Prx I-VI) with disparate chemical structures and activities. The disclosure details the identification of two specific peroxiredoxins, NKEF-A and -B, with putative antiviral activities. The disclosure does not describe the activities of any other peroxiredoxin species. The disclosure does not describe the preparation and characterization of any peroxiredoxin variants, or fragments thereof, that can reasonably be expected to retain the antiviral activity of the parent compounds. The disclosure fails to provide any guidance pertaining to the molecular determinants modulating the antiviral activity of any given peroxiredoxin. Thus, the skilled artisan has been asked to guess as to which of the inordinate number of variants might be useful as antivirals in the treatment of HIV-1 infection.

Applicants are reminded that the courts have concluded that generalized language may not suffice as a patent description if it does not convey the detailed identity of an invention. A description of what a material does, rather than of what it is, usually does not suffice. *Regents of the Univ. of Cal.* v. *Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1568 (43 U.S.P.Q.2d 1398) (Fed.

Cir. 1997). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. As the Supreme Court has cautioned, "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner* v. *Manson*, 383 U.S. 519, 536 (148 U.S.P.Q. 689) (1966). Here, the applicants have only identified two species that display *in vitro* antiviral activity. However, they are attempting to capture subject matter in an area where they have clearly failed to perform sufficient experimental work. Accordingly, the skilled artisan would reasonably conclude that applicants fail to meet the requirements set forth under this statute.

Applicants traverse and submit that claim amendments obviate the rejection. It was argued that the claims are now fully supported by the disclosure and that adequate structural information was provided. These arguments are not deemed to be persuasive. Contrary to applicants' assertions the claims still encompass a large genus of proteins that includes various naturally-occurring allelic variants, species variants, conservative amino acid substitution variants, and Prx fragments. While the disclosure provides a limited number of full-length Prx sequences and very limited structural guidance (i.e., the location of critical Cys residues), it fails to provide sufficient guidance pertaining to the various allelic variants, conservative amino acid substitution variants, and fragments that will display the desired activity. It is well-known in the art that single amino acid substitutions can alter the activity of any given enzyme in an unpredictable manner. Moreover, deleting various portions of an enzyme can render the molecule inactive. Furthermore, the Prxs encompass a large number of genotypically/phenotypically distinct members. For instance many members display different localizations (e.g., cytosolic, nuclear, mitochondrial, secretory) and have evolved to interact with different intracellular targets. Thus, the skilled artisan

cannot readily envisage the complete structure of most of the Prx variants that are encompassed by the claim language. Moreover, the disclosure fails to provide any further illumination on the subject. The disclosure only describes the isolation and characterization of two full-length human Prxs, NKEF-I and -9. Other allelic variants, conservative amino acid substitution variants, and fragments thereof with the desired activities are not disclosed.

Enablement

Claims 1-3, 18, and 19 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth *supra*, the claims have been amended and are now directed toward methods of treating HIV-1 infection through the administration of a peroxiredoxin. Perusal of the disclosure reveals that "peroxiredoxin" encompasses allelic variants, species variants, and conservative amino acid substitution variants. The term also encompasses various peroxiredoxin fragments" (pp. 10-11, bridging paragraph). The peroxiredoxin family encompasses a large and diverse number of sundry proteins (e.g., Prx I-VI) with disparate chemical structures and activities. The disclosure details the identification of two specific peroxiredoxins, NKEF-I and -9, with putative antiviral activities.

The disclosure describes the analysis of gene expression profiles of activated $CD8^+$ T-cells using a human cDNA expression array. It was observed that natural killer cell enhancing factors (NKEF) -A and -B were up-regulated in HIV-1-infected patients as compared to seronegative patients. The specification further reported that rNKEF-A and -B inhibited HIV-1 replication in an *in vitro* tissue culture assay. T-cell transfection studies revealed

that T-cells transfected with NKEF-A or -B were able to inhibit HIV-1 replication. Finally, elevated levels of NKEF-A and -B were observed in 23% of a small panel of HIV-1-infected, but untreated patients, who were long-term nonprogressors.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the molecular determinants modulating the antiviral activities of any given peroxiredoxin. Applicants traverse and submit that sufficient structural information is provided in the disclosure. This argument is clearly not persuasive. In order to fully appreciate and understand the invention, the skilled artisan would require a knowledge of those regions of any given peroxiredoxin that are *sine qua non* for the inhibitory activities of the protein. Simply noting that a particular Cys residue is required for activity does not provide any guidance pertaining to those critical determinants in the rest of the molecule. The Prxs vary in size between 198 amino acids to 271 amino acids. However, the disclosure fails to describe any mapping or mutagenesis studies to identify other critical regions. Which Prx amino acid

substitutions, additions, deletions, or fragments thereof will have the requisite activity?

2) The claims are broadly directed toward a large genus of compounds that includes peroxiredoxin allelic variants, species variants, conservative amino acid substitution variants, and fragments thereof. Applicants traverse and submit that the disclosure is fully enabling. This argument is not convincing. The Prx families include a large number of genotypically/phenotypically distinct members. At present, it encompasses human, murine, and bovine members of varying lengths (e.g., 198-271 amino acids) and tissue localizations (e.g., cytosolic, nuclear, mitochondrial, or secretory). However, the disclosure fails to provide sufficient guidance pertaining to the structural regions modulating the antiviral activities of the peroxiredoxins, which members of the family share these regions, and which portions of the protein can be modified in such a manner as to provide therapeutic activities.

3) The disclosure fails to provide any working embodiments. Contrary to applicants' assertions, the disclosure does not provide any working embodiments demonstrating that exogenously added Prxs can effectively reduce the viral burden associated with HIV infection and produce a positive clinical outcome. While it was noted that NKEF-A and -B displayed *in vitro* inhibitory activities, such simple tissue culture models are not generally considered to be predictive of clinical efficacy. While it was also reported that NKEF-A and -B were elevated in approximately 23% of a patient population that was not undergoing standard antiviral therapy. This finding is also hardly predictive of clinical success. First, the majority of patients failed to have elevated levels. Second, the patients appear to be long-term nonprogressors and are likely to be infected with an effete virus. Third, the fact that NKEF levels are elevated, does not demonstrate that this is responsible for the control of viral replication. The patients examined may simply have a robust immune response and humoral or cell-mediated

components may be responsible for the lack of disease progression. **4) The state-of-the-art vis-à-vis HIV-1 antiviral development is one of unpredictability.** Many promising antiviral agents have failed in the clinic because of several factors including the failure to adequately ascertain the pharmacological profile of any given compound beforehand, the quasispecies nature of HIV infection which leads to drug-resistance, the large quantities of virus present in the hematopoietic and lymphatic compartments, and the lack of adequate animal models with which to assess antiviral effectiveness (Gait and Karn, 1995; Yarchoan *et al.*, 1993; Back, 1999; Patience et al., 1994). The disclosure fails to address any of these caveats. Applicants' response fails to proffer any objective scientific data addressing the aforementioned concerns. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the claimed invention.

Finality of Office Action

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

27 November, 2004